

Gene by Environment Effects in Arsenic Metabolism: Genetic Polymorphisms with Differential Effects in Children

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For some time now, investigators have advanced the hypothesis that genetic determinants might underlie the individual variation in arsenic metabolism observed in numerous geographically diverse epidemiological studies. This could have important implications for disease susceptibility since arsenic metabolites have widely divergent toxic potencies, and signs of arsenicism have been associated with the distribution of urinary arsenic metabolites. The completion of the human genome sequence, together with new genetic experimental design approaches, have made comprehensively testing candidate genes for genetic association with arsenic metabolism a tractable problem. Here we report the results of a genetic association study that evaluated three candidate genes for arsenic metabolism: glutathione-S-transferase omega 1, purine nucleoside phosphorylase, and arsenic(3)-methyltransferase (AS3MT, formerly Cyt19).

Methods: One hundred thirty five subjects from western Sonora, Mexico, exposed to drinking water arsenic (5–43 parts per billion) were evaluated for arsenic species in their first-morning void of urine. Two phenotypes were evaluated: the ratio of inorganic arsenic (III) to inorganic arsenic (V) (3/5 ratio) and the ratio of dimethyl arsenic (V) to monomethyl arsenic (V) (D/M ratio). Subjects' DNA was analyzed for polymorphisms in the three candidate genes.

Results: Polymorphisms in one gene, AS3MT, were associated with D/M ratio in the entire population. Stratifying children (7–11 years of age) and adults (>18 years) revealed that the entire genetic association between AS3MT and D/M in the complete population arose from the children, in which the strength of the association was extremely high ($\sim 1 \times 10^{-6}$).

Conclusions: This is one of the first reports of a genetic effect that preferentially manifests in children and not adults. The results raise the possibility that a subset of arsenic-exposed children may represent a vulnerable subpopulation. (Supported by NIEHS ES004940)

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